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Assessment of FVIII, D-dimer, S. ferritin, and lactate dehydrogenase in hospitalized patients with 2019 coronavirus disease

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Abstract:

BACKGROUND: Corona virus disease 2019 (COVID-19) is a coronavirus that can produce a variety of symptoms, ranging from asymptomatic carrier status to severe respiratory failure, multiple organ dysfunction, and death, it might be associated with hypercoagulability as increase in coagulation factor 8 (FVIII).

OBJECTIVES: This study was carried out to investigate markers of hypercoaguablility (factor VIII activity, D-Dimer) in hospitalized adult patients with COVID-19, evaluation of certain markers of inflammation (S. ferritin, lactate dehydrogenase [LDH], C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]) and correlate those markers with each other.

PATIENTS AND METHODS: This cross-sectional study included 70 adult hospitalized patients with COVID-19. Blood samples were obtained for FVIII, D. dimer, and ESR. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 23 and Microsoft Office Excel 2010.

RESULTS: The mean age of enrolled 70 patients was 60.22 ± 14.43 years. 44 (62.9%) of patients had neutrophilia and lymphopenia was seen in 41 (58.6%). High ratio of N/L was seen in 66 (94.3%). Low count of eosinophil was seen in 44 (62.9%), high LDH level was seen at 57 (81.4%). Regarding serum ferritin, high level was seen 64 (91.4%) and high level of CRP was seen in 56 (80%). High level of ESR was seen in 64 (91.4%) and high level of D. dimer was seen in 55 (78.6%), while the high level of FVIII was seen in 30 (42.9%) and low FVIII level was seen in 4 (5.7%).

CONCLUSIONS: The majority of patients had neutrophilia, lymphopenia, high N/L ratio, and eosinopenia. Markers of inflammation (S. ferritin, LDH, CRP, and ESR), which were elevated. FVIII level and D. dimer were elevated in the majority of patients with COVID-19. Few of the patients were had a low level of FVIII, which might be related to abnormal function of the liver or might be attributed to autoantibodies directed against FVIII.

Keywords:

2019 coronavirus disease, D. dimer, erythrocyte sedimentation rate, FVIII

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Introduction

The 2019 coronavirus disease (COVID-19) can cause a wide range of symptoms, from asymptomatic carrier status to extreme respiratory failure, multiple organ dysfunction, and death. COVID-19 induces a special, deeply prothrombotic situation that contributes to both arterial and venous thrombosis, although it was originally believed to be exclusively a respiratory illness. Elevated D-dimer levels have repeatedly been established as an independent risk factor for poor outcomes, including death.[1] Furthermore, increased levels of D-dimer might be related to excessive inflammation due to cytokine storm and coagulopathy in COVID-19

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infection as a result that D-dimer represents the activation of coagulation suggesting extensive thrombin generation and fibrinolysis.[2,3]

Factor VIII increment as well as blood count irregularities such as neutrophil, lymphocyte, platelet, and neutrophil/lymphocyte ratio counts, have also been linked to a poor prognosis, probably as a result of their link to thrombosis. FVIII is a procoagulant factor that is contained in endothelial cells and released when they become inflamed. It is a cofactor in the tenase complex, which transforms factor X into activated factor X, and thus plays an important role in coagulation.[3]

Neutrophilia could be linked to a cytokine storm triggered by virus infection, and coagulation activation could be linked to a long-term inflammatory response.[4] Lympopenia in severe COVID-19 has been linked to a number of different pathways. Coronavirus (CoV) binding to the angiotensin-converting enzyme 2 (ACE2) receptor on lymphocytes, lymph node destruction, inflammatory cytokines, lactic acidosis suppressing cells, and direct lymphocyte inhibition.[5] The ratio of neutrophils to lymphocytes tends to be a marker of early inflammation and physiologic stress in the setting of lymphopenia.[6,7]

Patients and Methods

A cross-sectional study had been conducted on a total of 70 samples of hospitalized adult patients with COVID-19 admitted to the following hospitals: The 33 patients from Al-Imamian Al-Kadhimyain Medical city, 10 patients from Dar Al-Salam Hospital and 27 patients from Ibn Al-khatib Infectious Diseases Hospital, the sample was collected between November 22, 2020, and January 4, 2021. All patients included in this study were approved with positive polymerase chain reaction (PCR) for COVID-19 and randomly selected regarding age and sex.

Inclusion criteria

Hospitalized adult patients with COVID-19 proved by positive PCR.

Patients who have a history of D. M., chronic renal failure, malignant diseases, hemophilia A., other inflammatory conditions, and pregnant females were excluded.

The study was approved by the Institutional Review Board of the College of Medicine, Al-Nahrain University. Informed consent was obtained from all patients and their guardians before recruitment in the study.

Methods

A Peripheral venous blood sample (from the antecubital fossa) was withdrawn from all participants under aseptic technique, 4 ml of whole blood were collected and separated into 3 tubes: 1.8 mL poured into K2-EDTA tube for erythrocyte sedimentation rate (ESR) and 2 mL separated into two sodium citrate tubes, gently mixed, addressed with the name and the number of the participant and moved to the Teaching Laboratory in the Al-Imamein Al-Kadhimyein for investigation within <6 h after sample collection. For D-dimer measurements, the samples were taken from the patients with COVID-19, gently mixed and plasma was obtained after centrifugation for 15 min at 2500 g. STA Compact Max2 Coagulation analyzer was used to analyze blood samples from patients with COVID-19 from 33 patients from the Al-Imamein Al-Kadhimyein Medical City, while the results from 10 patients from Dar Al-Salam Hospital and 27 patients from Ibn Al-khatib Infectious Diseases Hospital provided from patients files.

For the determination of factor VIII activity in plasma, the samples were taken from the patients with COVID-19, gently mixed and then moved to a private lab in Baghdad for investigation within <6 h. For factor VIII measurements, plasma was obtained after centrifugation for 15 min at 2500 g. Then, for deep freezing, placed the samples in Eppendorf tubes in deep freezing reached (<−20–<−30), until the Factor VIII assay was done by STA®-Deficient VIII Kit using the Stago (STart Max), Diagnostica, USA.

Statistical analysis

Data were collected, summarized, analyzed and presented using the Statistical Package for the Social Sciences (SPSS) version 23 (IBM/Chicago USA) and Microsoft Office Excel 2010. Qualitative (categorical) variables were expressed as number and percentage, whereas, quantitative (numeric) variables were first evaluated for normality distribution using the Kolmogorov-Smirnov test, and then accordingly normally distributed numeric variables were expressed as mean (an index of central tendency) and standard deviation (an index of dispersion), while those numeric variables that are not normally distributed were expressed as median (an index of central tendency) and inter-quartile range (an index of dispersion).

Spearman correlation was used to evaluate the correlation between any 2 numeric variables and the results were expressed as correlation co-efficient ® and the level of significance (P).

The level of significance was considered at *P* value of equal or less than 0.05. The level of high significance was considered at *P* value of equal or less than 0.01.

Results

This current study included 70 patients with COVID-19, 22 (31.4%) females and 48 (68.6%) males,

the male-to-female ratio was 2.18:1. The mean age of enrolled patients was 60.22 ± 14.43 years and it ranged from 24 to 90 years. The mean hemoglobin level was 13.07 ± 2.38 g/dl and it ranged from 6.7 to 19.4 g/dl. The proportion of low hemoglobin (anemic patients) was 31 (44.3%) and the proportion of normal hemoglobin was 37 (52.9%) while the proportion of patients with polycythemia was 2 (2.8%).

The mean of the neutrophil count was $9.65 \pm 5.56 \times 10^9$/L and 44 (62.9%) patients had neutrophilia. The mean of lymphocyte count was $1.05 \pm 0.72 \times 10^9$/L and lymphopenia was seen in 41 (58.6%). The mean of N/L ratio was 13.30 ± 10.44, high ratio was seen in 66 (94.3%). The mean of eosinophil count was $0.04 \pm 0.11 \times 10^9$/L and the low count was seen in 44 (62.9%), the median level of LDH was 419.00 IU/L and high LDH level was seen 57 (81.4%). Serum ferritin median level was seen in 624.00 and high level was seen in 64 (91.4%). The median level of C-reactive protein (CRP) was 51.53 mg/L and high level was seen in 56 (80%). Regarding ESR, the median level was seen in 51.00 mm/h and high ESR was seen in 64 (91.4%). The median level of D-dimer was 1.44 µg/ml, high level was seen in 55 (78.6%), as shown in Table 1, while the median level of FVIII was 130.00% and the low FVIII level was seen in 4 (5.7%) and high level was seen in 30 (42.9%), as shown in Table 2. The mean hemoglobin level was higher in men in comparison with women, 13.65 versus 11.95 g/dl, in a highly significant manner ($P = 0.008$). In addition, serum ferritin mean level was higher in men in comparison with women, 656.50 versus 489.85 ng/ml, in a significant manner ($P = 0.017$). Moreover, the mean CRP level was higher in men in comparison with women, 63.30 versus 40.20 mg/L, in a highly significant manner ($P = 0.007$). The correlation of LDH and D. dimer were significant and highly positively significant ($P = 0.045$, 0.001), respectively, with N/L ratio. While, correlation of D. dimer and S. ferritin with neutrophil count were highly significant positively ($P \leq 0.001$, 0.003) respectively, and correlation of ESR with hemoglobin level was significant ($P = 0.015$), as shown in Table 3.

Table 1: The level of D-Dimer in patients with COVID-19

Characteristic	Results
D-Dimer (µg/ml)	
Median (IQR)	1.44 (3.10)
Range	0.10-16.00
Normal, *n* (%)	15 (21.4%)
High, *n* (%)	55 (78.6%)

n: number of cases; IQR: inter-quartile range

Table 2: The level of factor VIII in patients with Covid-19

Characteristic	Results
FVIII %	
Median (IQR)	130.00 (95.50)
Range	24.00-490.00
Low, *n* (%)	4 (5.7%)
Normal, *n* (%)	36 (51.4%)
High, *n* (%)	30 (42.9%)

Table 3: The haematological characteristics and markers of inflammation according to gender

Characteristic	Male *n*=48	Female *n*=22	*P*
Haemoglobin (g/dl)	13.65 (2.47)	11.95 (1.97)	0.008**
Neutrophil	9.05 (6.93)	8.58 (6.28)	0.990
Lymphocyte	0.80 (0.79)	0.82 (0.97)	0.314
NLR	12.26 (13.35)	7.55 (7.2)	0.349
Eosinophil	0.00 (0.05)	0.01 (0.06)	0.555
Platelet	245.00 (164.50)	278.00 (188.50)	0.204
LDH (U/L)	407.00 (335.25)	457.50 (430.50)	0.800
D.Dimer (µg/ml)	1.48 (3.74)	1.34 (2.48)	0.840
Serum ferritin (ng/ml)	656.50 (364.20)	489.85 (545.72)	0.017*
CRP (mg/L)	63.30 (83.64)	40.20 (42.62)	0.007**
ESR	53.00 (31.75)	49.00 (37.75)	0.621
FVIII %	127.00 (82.25)	160.00 (165.75)	0.904

*Significant at $P \leq 0.05$; **highly significant at $P \leq 0.01$

Discussion

The novel severe acute respiratory syndrome CoV 2 (SARS-CoV-2) tends to establish a profoundly prothrombotic environment, as demonstrated by a rise in reports of arterial, venous, and catheter-related thrombosis around the world.[1] A novel CoV, SARS-CoV-2, elicited an acute inflammatory response that might result in hypercoagulability, platelet activation, and endothelial dysfunction.[8] Factor (F) VIII is a procoagulant factor that is stored in endothelial cells and released during inflammation. It was a cofactor in the tenase complex, which transforms factor X into activated factor X, and thus played an important role in coagulation.[3] In patients with COVID-19 found that there is increase level of FVIII in several studies which might be linked to hypercoagulability. The low FVIII level was seen in (5.7%) of our cases, normal level was seen in (51.4%) and high level was seen in (42.9%). The result of high level was comparable with many other studies,[3,9-11] but our median of FVIII was differed.

The increase in Factor (F) VIII might be a mirror of the systemic endothelial damage recently described in COVID-19. FVIII was one of the most potent triggers of hypercoagulability, and pro-coagulant FVIII levels were increased in patients with severe symptoms.[12-14] As a result, a high level of FVIII, which is reported as an acute phase reactant, might be linked to pro-inflammatory cytokines as a result of cytokine storm, contributing to the hypercoagulable status of those COVID-19 patients and might be to the procoagulant imbalance in COVID-19 patients.[11,13,15,16] Regarding low FVIII level

was seen in (5.7%) in our study was compared with Rauch *et al*.,[17] which showed a drop in FVIII levels on admission was related with a higher likelihood of worsening respiratory state, as demonstrated by an increase in oxygen requirements, in a study of COVID-19 patients with varied degrees of illness. The changes in FVIII levels might be linked to inflammation in a liver that has been damaged by pro-inflammatory cytokines. While this result might be attributed to autoantibodies directed against FVIII that was rare acquired bleeding disorder that lead to Acquired hemophilia A.[18,19] Regarding D-dimer, the normal level was seen in (21.4%) whereas high level was seen in (78.6%), this was in agreement with other study.[20] This result of elevation in D-dimer might be related to dysregulated hemostasis and that elevation was used as indicators of disease progression.[21,22] Furthermore, increased levels of D-dimer might be related to excessive inflammation due to cytokine storm and coagulopathy in COVID-19 infection as a result that D-dimer represents the activation of coagulation suggesting extensive thrombin generation and fibrinolysis.[2,3]

Regarding complete blood count parameter the study showed that the proportion of low hemoglobin (anemic patients) was (44.3%) and the proportion of normal hemoglobin was (52.9%) while the proportion of patients with polycythemia was (2.8%), this result was in agreement with many other studies from Iran, Singapore, Wuhan, Spain and Italy.[11,23-29]

Low level of Hb. might be SARS-CoV-2 might induce the Inflammation-driven increase in hepcidin concentrations which blocks the correct use of iron, increasing ferritin while inducing serum iron deficiency and a decline of Hb. level.

Regarding neutrophil count in this study, the normal neutrophil count was reported in (37.1%) patients while (62.9%) patients had neutrophilia. The mean of our result was in agreement with some studies.[23,30] Neutrophilia was comparable to many other studies.[23,31,32]

This neutrophilia might be related to an expression of the cytokine storm and hyperinflammatory state which have an important pathogenetic role in COVID-19, and it is might increased risk of ARDS and death, also the levels of neutrophils have been suggested to reflect the inflammatory state during disease progression.[25,27,33]

Regarding lymphocyte count, lymphopenia was seen in (58.6%), normal count was seen in (38.6%) and lymphocytosis was reported in (2.9%), this was in agreement with many other studies,[11,32] and Du *et al*.,[30] who showed that totals of 66 (77.6%) of the patients had lymphocytes below the normal range. Furthermore, Tan *et al*.'s study, which showed lymphocyte count of severely involved patients decreased.[34]

Regarding lymphocytosis in our results, this was in agreement with other studies in Malaysia and India and this might be associated with a milder disease.[5,35]

Lymphopenia might be due to a defective immune response to the virus and associated with the amplification of the inflammatory process (cytokine storm syndrome) and might be related to direct lymphocyte inhibition because of direct infection of lymphocytes and lactic acidosis destroying lymphocytes and coronavirus attaching to the ACE2 receptor on lymphocyte and related to disease severity.[5,36-39]

Regarding neutrophil-to-lymphocyte ratio (NLR), normal ratio was seen in (5.7%), whereas the high ratio was seen in (94.3%), this was in agreement with Yang *et al*.[31] However many other studies revealed that NLR is a useful systemic inflammation marker for screening COVID-19 infected patients.[27,40,41]

Concerning eosinophil count, low eosinophil count was seen in (62.9%), normal count was seen in (35.7%) and high count was seen in (1.4%). This result was in agreement with other study.[42] Du *et al*. showed 69 (81.2%) patients from 85 patients had an eosinophil count below the normal range.[30] Eosinopenia might be linked to eosinophil egress inhibition, eosinophilopoiesis blockade, and reduced expression of chemokine receptors/adhesion factors, and the decrease in eosinophils might be linked to a stress response mechanism in the case of acute lung injury caused by SARS-CoV-2, which inhibit the release of eosinophils in the marrow.[31,42-44]

Regarding serum ferritin, normal level was seen in (8.6%) and high level was seen in (91.4%), this result was in agreement with a study from China.[45] Ferritin level is a marker of inflammation and it is an important factor affecting the severity of COVID-19. Hence, the high level of ferritin might be harmful effects on mitochondria, leading to the release of reactive oxygen species, which cause cell death.[46,47]

Concerning LDH, normal LDH was seen in (18.6%) and high LDH level was seen in (81.4%), this results in agreement with many other studies.[23,32,48] High LDH level might be related to damage to any cells in almost all organ systems that normally express LDH and elevation in LDH was common in COVID-19 patients and might be related to cytokine-mediated tissue damage due to COVID-19 infection and it is used as indicators of disease progression.[22,35,49,50]

Regarding CRP in the current study, normal CRP was seen in (20%) and high level was seen in (80%). This result

was in agreement with some studies.[29,45,51] The CRP, which is produced by the liver and it is an acute-phase reactant that is produced by the liver. So, increased its level in a wide range of inflammatory conditions and in response to inflammation due to COVID-19 infection, particularly in severe cases.[35,49]

Regarding ESR, normal ESR was seen in (8.6%) and high ESR was seen in (91.4%). This result was agreed with other study.[24] However, ESR can be used as a powerful indicator to predict disease severity in SARS-CoV-2 infected patients.[52]

In the current study, we concluded that hemoglobin level, S. ferritin, and CRP were higher in men in comparison with women, in a highly significant manner. Regarding hemoglobin level (P = 0.008) comparable to study from Iran, but their study was not significant.[28] The correlation of LDH and D. dimer with N/L ratio was highly significant positive and also, correlation of D. dimer and S. ferritin with neutrophil count were highly significant positively. it was in agreement with Zhang *et al*.[53] and Yazdanpanah *et al*.,[54] respectively. The correlation of ESR with hemoglobin level was significant.

Conclusions

From this study, it can be concluded that the majority of patients had neutrophilia, lymphopenia, high N/L ratio, and eosinopenia. Markers of inflammation (S. ferritin, LDH, CRP, and ESR), which were elevated. Moreover, FVIII level and D. dimer were elevated in majority of patients with COVID-19. This elevation might be related to dysregulated hemostasis and pro-inflammatory cytokines and contributes to the hypercoagulable status of those patients with COVID-19. Few of the patients were had a low level of FVIII, which might be related to abnormal function of the liver or might be attributed to autoantibodies directed against FVIII.

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Conflicts of interest

There are no conflicts of interest.

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